Heart as a Muscle

Introduction

Cardiac muscle cells, cardiac **myocytes**, are commonly taught alongside skeletal muscle myocytes and smooth muscle myocytes. We taught skeletal muscle myocytes in the General Physiology module in order to link action potentials, neurotransmitters, and ionotropic receptors to clinical disease. We also purposefully separated skeletal muscle and skeletal muscle disease from smooth muscle. We will absolutely draw from your knowledge of skeletal muscle myocytes in this lesson, specifically sarcomeres. Cardiac myocytes use the **same sarcomeres as skeletal muscle**, with a little extra that we will discuss in this lesson. Because the sarcomeres are the same, much of the physiology is the same, so we will not be spending much time on sarcomeres. HOWEVER, **sarcomeres are the ONLY thing in common** between skeletal muscle myocytes and cardiac myocytes. Obviously, there are many similarities, like the use of ATP, cellular respiration, DNA, etc., etc. The purpose of being so overbearingly hyperbolic is to ensure that you do not conflate your deep-seated knowledge of skeletal muscle myocytes and cardiac myocytes. Everything of import is different. **Even the sarcomeres are different.** We chose not to teach cardiac myocytes with skeletal muscle myocytes for exactly this reason. We will be repeating things you already know so that you create new memories regarding cardiac myocytes that are siloed, separate, and nowhere near skeletal muscle myocytes.

We will talk about cardiac myocytes—their histology and connections to one another, and how they generate the force of contraction. The force of contraction contributes to the stroke volume. The components of stroke volume in our MAP equation are preload and contractility. We want you to associate **preload** with **sarcomere length** and **contractility** with **calcium channels**. We're adding another synonym to each box in the MAP equation and will explore these new synonyms in great detail. This information is necessary to understand the normal and abnormal for the rest of the Structure and Function module.

Myocyte Structure

This section focuses on the one, singular myocyte. The formation of the syncytium—the unit of coordinated but independent myocytes—is detailed later.

Cardiac myocytes shorten and lengthen, generating a force of contraction as actin slides over myosin, driven by intracellular calcium—cardiac myocytes have **sarcomeres**. Having sarcomeres, cardiac myocytes appear to be **striated** on histology. Cardiac myocytes have eosinophilic (**pink**) cytoplasm and a basophilic (**blue**) nucleus located in the **center of the cell**. Each cardiac myocyte has its own nucleus. The myofibrils of the sarcomere separate at the nucleus, where most of the other organelles are located. Cardiac myocytes must contract many times per minute (normal heart rate is 60–100 bpm). Contraction requires a significant amount of energy (ATP). Because there is so little downtime and so much activity, cardiac myocytes don't have time to make glycogen. That means cardiac myocytes require a lot of cellular respiration. To accomplish this, cardiac myocytes have **many mitochondria** and **high oxygen extraction**. The many mitochondria use the glucose and oxygen in the blood to perform glycolysis, citric acid cycle, electron transport chain. The heart has the highest oxygen consumption of any tissue (80% of oxygen is taken from the blood flowing through the coronary arteries). To supply the necessary oxygen and glucose, every single myocyte is in contact with at least three capillaries. This is vastly different from other tissues, in which one capillary services multiple cells.

Cardiac myocytes are **individual cells** that act in a coordinated fashion—they make a **syncytium**. Depolarization leads to contraction. Depolarization occurs in a coordinated fashion, from the apex up, ensuring a coordinated, sequential contraction that pushes the blood up and out through the outflow tract. The ventricle does not contract to bring two points together, rather it squeezes from the bottom up

(imagine squeezing a full tube of toothpaste really hard from the bottom). The myocytes are a syncytium; they are coordinated, and yet they are independent cells. They maintain connections to one another via **intercalated discs**. A dense discussion follows in the next section, but the histological consequence is the appearance of **densely eosinophilic** bands **perpendicular** to the longitudinal array of fibrils and parallel to the striations. The myocyte is pale pink on H&E, the striations slightly darker pink (within the myocyte), and the intercalated disks the darkest pink and most conspicuous (the myocyte's border).

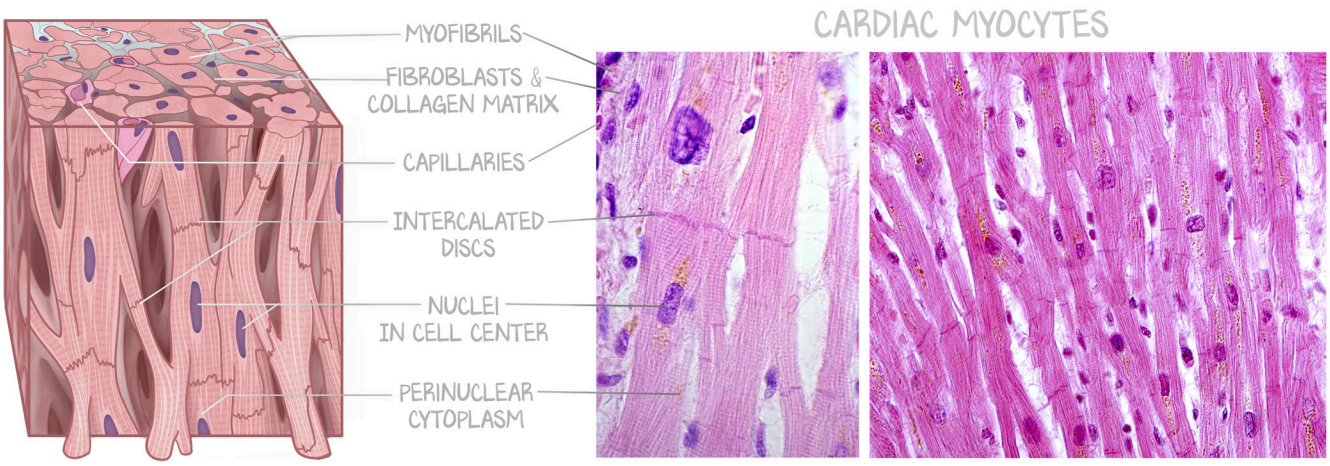

Figure 4.1: Cardiac Myocytes
This is a warmup figure. The illustration shows cardiac myocytes both in longitudinal section and in cross-section, detailing the elements on histology. Notice the central nucleus, striations, and intercalated discs. The histology shows the same thing—central basophilic (blue) nucleus, eosinophilic (pink) cytoplasm with striations, and a conspicuous intercalated disc at the edge, connecting two myocytes together.

Myocyte Connections: Intercalated Discs

Intercalated discs appear as darkly staining bands that are perpendicular to the length of the myocyte and parallel to the striations. All of the myocytes run in the same direction on a slide, called a longitudinal arrangement. The myofibrils, sarcomeres, and cells themselves run in the same direction. The intercalated discs are perpendicular to that arrangement, called a **transverse arrangement**. On light microscopy, intercalated discs appear to be only transverse, perpendicular to the longitudinal arrangement.

On electron microscopy, the intercalated discs get more complicated. You were just told about transverse (perpendicular to the fibrils, parallel to striations) and longitudinal (parallel to fibrils, perpendicular to striations). Intercalated discs are actually a zig-zag of **transverse components** (perpendicular to the fibrils, parallel to the striations) and **lateral components** (which should be longitudinal components, parallel to fibrils, perpendicular to striations). Transverse and lateral are the names these structures have; the transverse components match the transverse arrangement, whereas the lateral components match the longitudinal arrangement.

Follow along with Figure 4.2 as you progress through the next several paragraphs.

Said differently, the myofibrils, particularly actin, run into the transverse component and pass by the lateral component. This is important because the **actin filaments attach to the transverse** component via a modified adherens junction (more below). The cytoplasm of neighboring cardiac myocytes is continuous through an extensive network of gap junctions. The **myocytes' cytoplasm is continuous through gap junctions** located in the **lateral** component. The transverse component has specialized adherens junctions; the lateral has gap junctions. Both also contain desmosomes.

The **transverse component** of the intercalated disc crosses the myofibrils perpendicularly. The sarcomeres are effectively continuous from one myocyte to the next due to **adherens junctions** (also referred to as the fascia adherens), the **anchor for sarcomeres** at the edge of the cell. The terminal actin filaments of neighboring myocytes' sarcomeres connect to these adherens junctions. You've seen a similar arrangement before, in General Physiology #9: *Epithelium.* Neighboring cells of an epithelium let each other know that the epithelium is intact via extracellular cadherin proteins that interact with each other. This adherens junction is just like that, except there aren't extracellular proteins from either cell; the cells share these proteins between them, embedded in their plasma membranes. Each transmembrane cadherin protein spans the plasma membrane of a myocyte, the intercellular space, and the plasma membrane of its neighbor. Intracellularly, catenin connects to the terminal actin fibers of the terminal sarcomere, turning **the transverse component of the intercalated disc into an effective intercellular Z line**. In this sense, the contractile elements of one myocyte are continuous with the contractile elements of its neighbor, as if they were one continuous cell with one continuous chain of sarcomeres.

In addition to this effectively seamless structural transition from sarcomere to sarcomere across plasma membranes, there is also an electrochemical connection. The **lateral component** is at a right angle to the transverse component, parallel with the myofibrils. The lateral component consists almost entirely of **gap junctions**. Gap junctions connect the cytoplasm of neighboring myocytes, allowing for the immediate communication of electrical impulses and ions. The density of gap junctions at the intercalated disc is astounding. We discuss them and their relation to cardiac conduction in Electricity #2: *Conduction System*. But effectively, just as the transverse components make the sarcomeres continuous, the **gap junctions make the cytoplasm continuous** and serve as the mechanism for subsequently coordinated depolarization.

But if that were all, they could potentially rip away from each other every time they contract. That means there must be something holding the cells together—some intracellular connection that is discontinuous but really strong—allowing them to contract as one common muscle fiber, even though they are separate cells. You've seen these before, too: **desmosomes**. The intercalated discs have sporadic desmosomes (maculae adherentes; singular, macula adherens) on both the lateral and transverse faces of the intercalated discs. These are sporadic but numerous and serve to hold the cells together. Be careful with the terminology—adherens junction, fascia adherens, and zona adherens describe the things that use catenin-cadherins; macula adherens describes desmosomes.

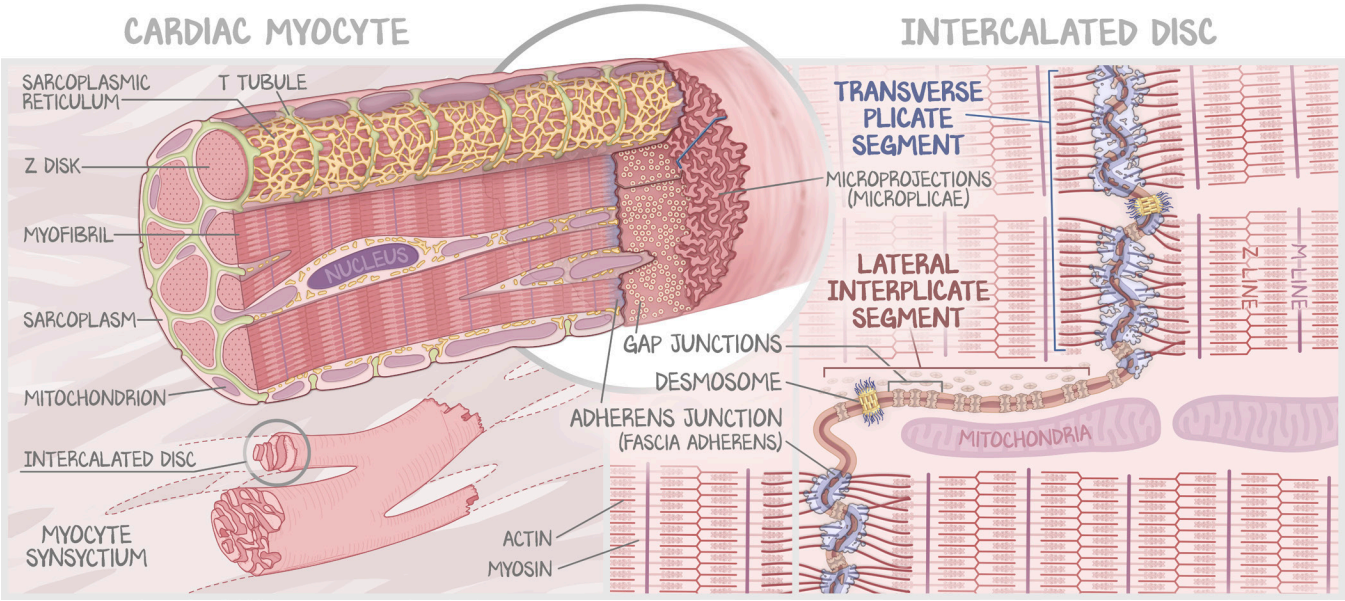

Figure 4.2: Cardiac Myocyte Intercalated Disc

The force of contraction of the heart is dependent on the force of contraction of the individual sarcomeres. Generating more force of contraction, from the perspective of sarcomeres, comes down to **optimizing sarcomere length** (aka preload, volume, Na^+, aldosterone) and **activating more calcium channels** (β_1, calcium channels, calcium conductance).

Force of Contraction: Sarcomere Length (aka Preload, Volume, Na+, Aldo)

Yay! More similarities! More detail is found in General Physiology #14: *Skeletal Muscle Force*. But there's a twist. The amount of force created by a contraction depends on how much actin slides over myosin with each contraction. The gist is that there is a maximum force generated in a given sarcomere where there is both the ideal overlap of actin and myosin to generate force and the ideal room for actin to slide in. This change in sarcomere length is the greatest possible, generating the greatest force of contraction. The best arrangement for a maximal force of contraction is the perfect balance of overlap and room to move.

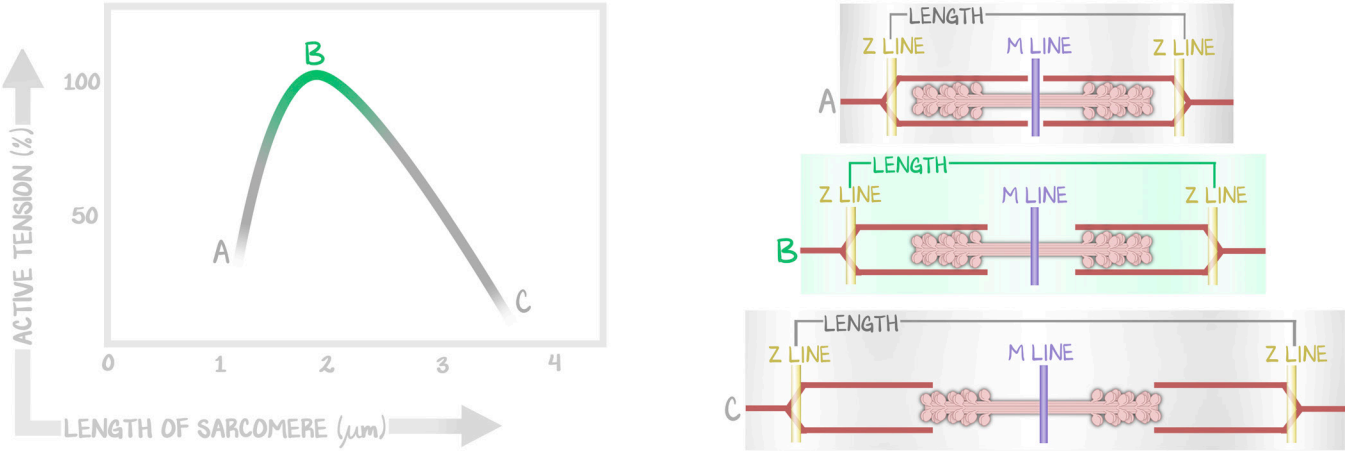

Figure 4.3: Sarcomere Length and Force of Contraction
(a) A sarcomere that is too short maximizes the actin and myosin overlap, but there is nowhere to slide. (b) The sweet spot of overlap and room to slide that maximizes contraction. (c) Here, there is plenty of room to slide, but there isn't enough overlap to generate force. This is a reproduction of Figure 14.1 from General Physiology #14: *Skeletal Muscle Force*.

Cardiac myocytes never go past their optimal length. Cardiac myocytes never go past their optimal length because of titin. **Titin** gets its name from its size (the protein's namesake, Titan, is very large), but that doesn't help you know what it does. The mechanism is not well elucidated and very complex, so we want you to learn what it does with an analogy. Think of titin as a spring. The farther from the M line the Z lines get, the longer the sarcomere becomes, the more coiled titin becomes. As the sarcomere length approaches the optimal length, titin continues to store more and more tension, preventing the sarcomere from lengthening further. Then with depolarization, not only is there actin and myosin overlap, but the tension stored in the titin molecule is released as well.

Because titin prevents the sarcomeres from passing the optimal length, any lengthening of the sarcomere will prepare a stronger force of contraction. Because titin stores more tension the longer the sarcomere gets, titin will add more force of contraction the longer the sarcomere becomes. **Both the optimization of length** and the **tension stored by titin** ensure that maximum tension will be achieved, growing with the increased length of the sarcomeres. The way to **increase sarcomere length** in the heart is to **add volume** (aka preload, Na^+, aldosterone).

And so, "*the more blood into the heart, the more blood out of the heart*." Increasing preload will increase the volume of blood ejected. We haven't defined "ejection fraction" yet, and will in the lessons to come, but a normal ejection fraction is 55%. The function of the left ventricle is expressed as a percentage, not a volume. The volume ejected during systole is approximately half of the volume in the ventricle during diastole.

he cardiac myocytes are very similar, except that because the heart is always beating, their sarcomeres are always either shortening (systole) or lengthening (diastole). Therefore, the sarcomeres in cardiac myocytes have learned to operate in a narrower range of sarcomere length. Explaining this takes a lot of effort, so take it on faith that **active tension of cardiac sarcomeres necessitates a narrow range of sarcomere length**. If they lengthen too far in diastole, the force of contraction is compromised. If they don't lengthen enough, the force of contraction is compromised.

At physiological volumes, any increase in ventricular volume will better optimize sarcomere length and titin tension. The more blood in the heart, the farther the sarcomeres stretch, the more optimized the sarcomeres become and the higher the titin tension, the more forceful the contraction, the more blood out of the heart. This has many implications that we're saving for the next lesson. For now, learn: more volume in, more volume out.

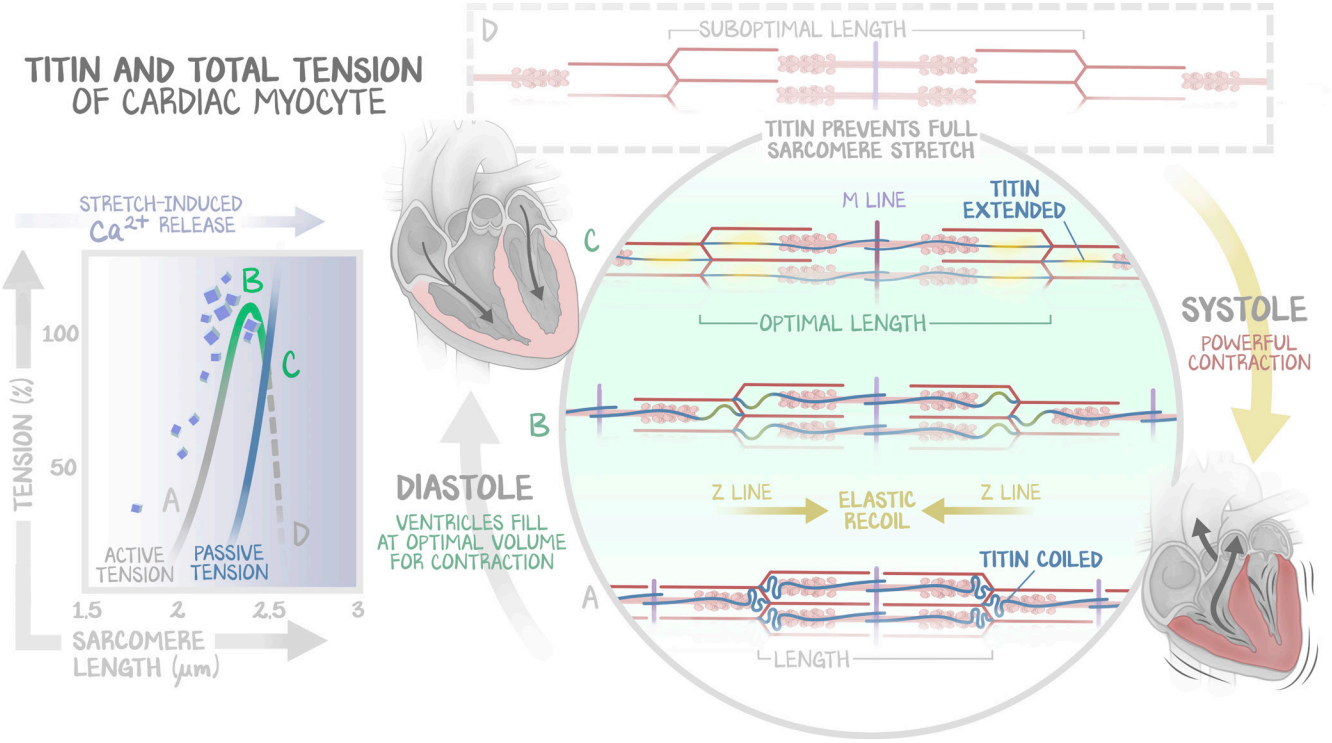

Figure 4.4: Total Tension of a Cardiac Myocyte
Total tension in cardiac muscle is the sum of active and passive tension, just as in skeletal muscle. However, cardiac muscle cannot be explained simply by the overlap of actin and myosin alone because of the very narrow window of sarcomere length, which results in drastic variations in cardiac forces. (b) Stretch causes calcium release and optimizes sarcomere length. (c) Titin resists distension, preventing the sarcomere from passing optimal overlap. Any passive tension stored by titin contributes to the total tension, to the shortening of the sarcomeres.

Force of Contraction: Calcium-Induced Calcium Release

The **sarcolemma** is the plasma membrane of a myocyte. The **sarcomere** is the functional contractile unit of the myocyte. Sarcomeres are stacked one on top of the other, longitudinally arranged along the length of the myocyte. The **sarcoplasmic reticulum** is the smooth endoplasmic reticulum of myocytes and contains calcium. **T tubules** are invaginations of the sarcolemma that travel through the myocyte, between myofibrils. The T tubules are intimately associated with the sarcoplasmic reticulum as a **diad junction** (not a triad). As electrical impulses travel down the sarcolemma of a myocyte, they also travel down T tubules, propagated by sodium influx. The voltage change opens L-type Ca^{2+} channels in the sarcolemma.

Your brain has naturally drifted to skeletal muscle physiology because all of that sounds awfully similar to skeletal myocytes. Same words. Same structures . . . oh, but a diad! . . . It was all the same. But pay close attention to what happens next. Because just as cardiomyocytes share one point of anatomy (striations) but nothing else with skeletal muscle, they also share one physiological similarity: excitation-contraction coupling.

L-type Ca^{2+} channels are **voltage gated**. They open with depolarization. They stay open as long as the membrane is depolarized. Calcium enters the cell (the same as in skeletal myocytes, but here comes the difference). The sarcoplasmic reticulum contains channels called **ryanodine receptor 2 (RyR2) calcium channels**. These receptors use **calcium as a ligand**. Calcium influx from L-type channels leads to the opening of RyR2s, leading to a massive influx of calcium from the sarcoplasmic reticulum. This **calcium-induced calcium release** floods the cytoplasm with calcium. The mechanisms by which the calcium signal is turned off and calcium is put back in the sarcoplasmic reticulum are beyond our scope. But notice what is very different here in cardiac myocytes. The same voltage-gated L-type calcium channel as in skeletal myocytes opens on the plasma membrane, but it is not the mechanically associated ryanodine receptors (RyR1) that open. Rather, the calcium influx acts as a ligand for RyR2 channels, which then open via receptor mediation.

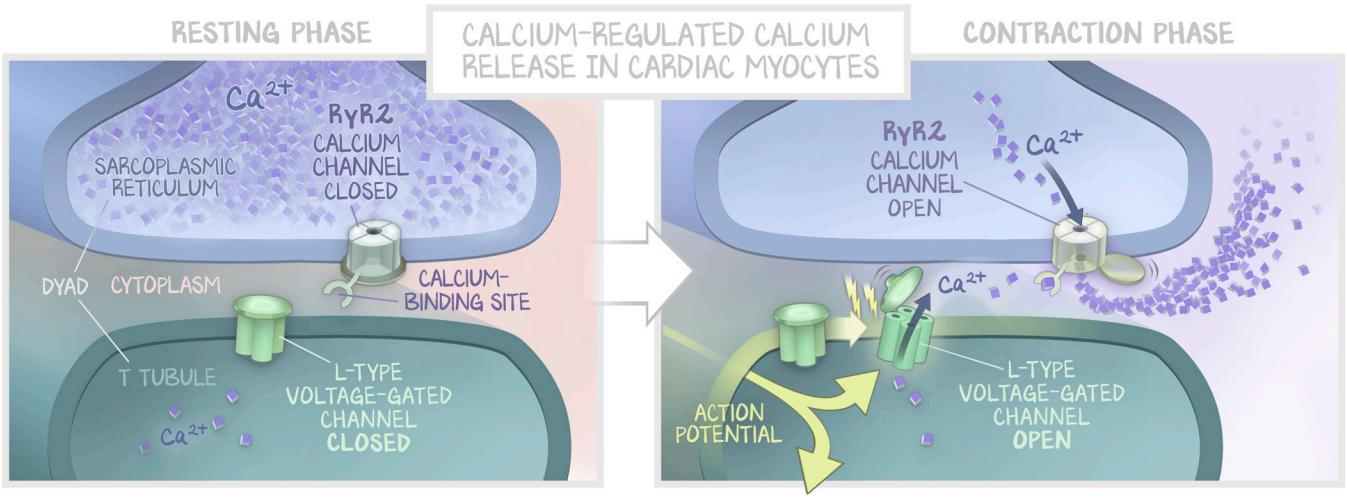

Figure 4.5: Calcium-Regulated Calcium Release
In the resting phase, L-type voltage-gated channels are closed, just like in skeletal muscle. The RyR2 calcium channels—calcium receptors that are also calcium channels—are closed, and lots of calcium is in the sarcoplasmic reticulum. When the plasma membrane depolarizes, the electrical change opens the L-type voltage-gated channels, and calcium enters the cytoplasm from the extracellular space. That calcium binds to and activates the RyR2 calcium channels, opening a pore for all the calcium in the sarcoplasmic reticulum to flow into the cytoplasm.

Calcium Initiates Contraction of Cardiac Myocytes

Yay! More similarities! More detail is found in General Physiology #12: *Skeletal Muscle Excitation Coupling*. The mechanisms of calcium, actin, and myosin in cardiac muscle should be learned as identical to those of skeletal muscle. We don't want you comparing skeletal muscle to cardiac muscle. We don't want you building tables. But we're definitely going to harness the fact that this process is the same as in skeletal muscle to just move through it.

Thick filaments are myosin—heavy chains and light chains. Thin filaments are actin. Myosin-binding sites on actin filaments are covered by tropomyosin. Troponin C (TnC) binds calcium, inducing a conformational change in tropomyosin. This moves troponin I (TnI) off the myosin-binding site on actin. Myosin is then allowed to bind to actin. ATP fuels the subsequent cross-bridge cycling.

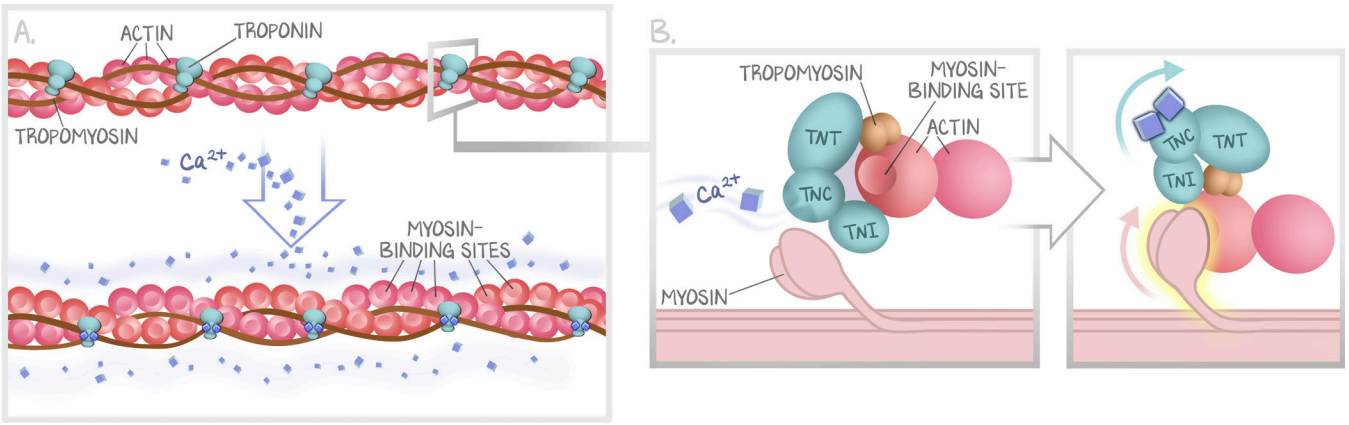

Figure 4.6: Calcium and Actin
Binding of calcium to TnC induces a conformational change that rolls the entire tropomyosin complex away from the myosin-binding site, allowing myosin to bind to actin and initiate the powerstroke. This is the same illustration as Figure 12.3 from General Physiology #12: *Skeletal Muscle Excitation Coupling*.

Force of Contraction: Sympathetics (aka Contractility, β1, Heart)

The more calcium conductance, the more calcium there will be in the cytoplasm, and the stronger the force of contraction. The **sympathetic** nervous system innervates the cardiac myocytes of the ventricles. Acting through **β_1 receptors**, the sympathetic nervous system **increases calcium conductance** and, therefore, induces a larger force of contraction. We're intentionally ignoring the mechanism of heart rate control (which both the parasympathetics and sympathetics innervate), focusing here on the force of contraction.

β_1 receptors are G protein-coupled receptors that utilize the G_s-AC-cAMP-PKA pathway. The net result is stronger Ca^{2+} conductance, stronger Na^+ conductance (depolarizes more powerfully), and lower K^+ conductance (repolarizes more easily). We get into the significance of sodium and potassium in the Electricity island. More calcium and calcium conductance mean more calcium influx, and more calcium influx means more activation of RyR2 calcium-induced calcium release and more calcium in the cytoplasm. **More calcium, more force.**

CHARACTER	PARASYMPATHETIC	SYMPATHETIC
Ligand	Acetylcholine	Norepinephrine
Receptor	M_2	β_1
G protein	G_i	G_s
Intracellular pathway	AC-cAMP-PKA inhibition	AC-cAMP-PKA stimulation
SA node	Lower chronotropy (slower HR)	Higher chronotropy (faster HR)
AV node	Slows conduction velocity	Accelerates conduction velocity
Ventricles	N/A	Stronger contractions

Table 4.1: Autonomics Review
The key here is that the autonomics provide physiological antagonism at the nodes, but there is NO parasympathetic tone at the ventricles, only sympathetic.

Myocytes contract all at once and relax all at once. **Temporal summation**—multiple action potentials that increase calcium prior to a contraction—can't work for cardiac myocytes. Depolarization of one pacemaker myocyte depolarizes the syncytium. **Recruitment**—summoning increasingly large motor units—can't work for cardiac myocytes. All of the myocytes contract with every heartbeat. Therefore, the only way the **heart increases contractility** is by **increasing calcium conductance** with every depolarization, and the mechanism by which that is done is β_1 receptors.

Summary of Where We're At

Thought you could get away from it because we didn't put it at the beginning of the lesson. Huzzah! The MAP equation! We didn't talk about SVR or afterload this time because what we were after was stroke volume. We didn't tell you that, we just showed you how increased preload and increased contractility lead to a "stronger force of contraction." Well . . . this is the mathematical equivalent of "*more blood in, more blood out.*" If preload and contractility go up, what happens to stroke volume? It goes up! We also didn't talk about heart rate because that only contributes to cardiac output, not stroke volume. And it's just a per-minute multiplier, anyway. The next lesson will incorporate systemic vascular resistance into the MAP (uh, WORK, uh, FORCE) equation.

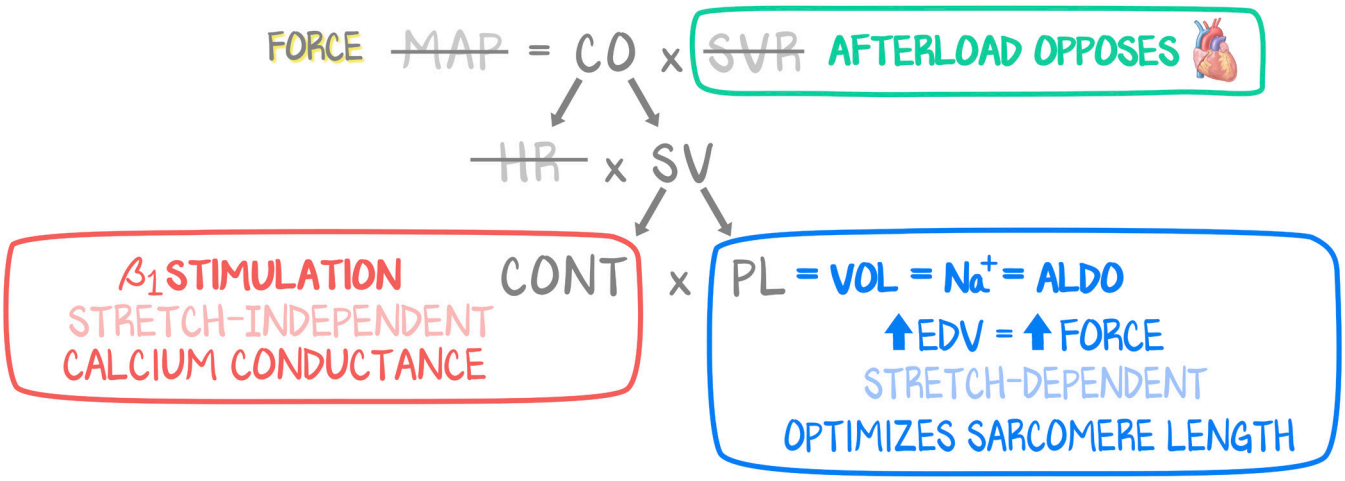

Figure 4.7: Map Equation
The force of contraction equation is the MAP equation (and will be the myocardial work equation). By simply changing the names but keeping the colors, we're transitioning you through the several layers of cardiac physiology (and soon pathophysiology) in a way you won't see elsewhere. Seeing the MAP equation, using it as a map, helps keep new concepts, new ways of thinking, attached to the same organizer you know well.

If you're comfortable with this next paragraph, then you are in a really good place for the remainder of the Structure and Function island. If you aren't, watch the video, do the questions, then circle back to this paragraph. If you still aren't comfortable, do the lesson again. If you have this information down cold, the next few lessons are a breeze.

Cardiac myocytes are individual cells, each with one nucleus. They have the familiar sarcomere arrangement found in skeletal muscle. But because they are individual cells, their interaction necessitates additional complexity. The transverse component of the intercalated disc has desmosomes to hold the cells together and a common anchor for the actin filaments of neighboring myocytes (adherens junctions), allowing them to contract as one syncytium. The longitudinal component of the intercalated disc has desmosomes to hold cells together and a massive density of gap junctions that effectively make the cytoplasm of all the myocytes of a syncytium one big cytoplasm. Depolarization from a pacemaker myocyte (you haven't learned the details of this yet) depolarizes the syncytium. Depolarization results in calcium influx across the plasma membrane. This calcium enters the cytoplasm and binds to RyR2 channels, which causes a massive influx of calcium into the cytoplasm. This calcium does what it does to actin and myosin in any myofibril, identical to skeletal muscle. Sarcomeres shorten, the syncytium shortens, contraction occurs. Contraction ends, and sarcomeres are stretched by both the passive relaxation of myofibrils and the active pressure applied by incoming blood. The sarcomeres are arranged so that any physiological increase in ventricular size (any additional preload) will only serve to optimize sarcomere length further—more blood in the heart, more blood out of the heart. A normal heart cannot be overstretched because titin won't allow it. Therefore, the only way to modulate ventricular force is to add volume (preload) up to a point (because further stretch is prohibited by titin) or to increase cytoplasmic calcium (β_1 receptor activation).